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(54) Pharmaceutical composition and method for treating hyperlipidemia and arteriosclerosis

Pharmazeutische Zusammensetzung und Methode zur Behandlung von Hyperlipidämie und Arterioskerose

Composition pharmaceutique et méthode pour le traitement de l'hyperlipémie et de l'arteriosclérose

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- **AMERICAN JOURNAL OF PATHOLOGY vol. 139, no. 1, 1 July 1991, pages 217 - 229 MCGUIRE E.J., ET AL., 'Peroxisome induction potential and lipid-regulating activity in rats'**
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- **INT. J. OBES. vol. 11, 1987, pages 619 - 629 F.M. WHITTINGTON ET AL. 'Effect of sodium 2-n-pentadecyl-benzimidazole-5-carboxylate (M & B 35347B) an inhibitor of acetyl-CoA-carboxylase, on lipogenesis and fat deposition in obese hyperglycaemic (ob/ob) and lean mice'**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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Description

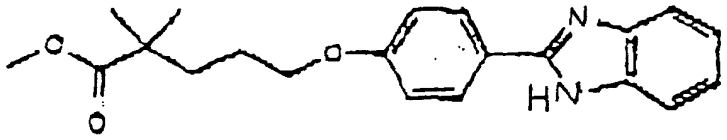
Background of the Invention

[0001] The present invention relates to a novel pharmaceutical composition and method for treating hyperlipidemia and arteriosclerosis, more specifically to an antihyperlipidemia agent having a blood cholesterol lowering effect or an antiarteriosclerosis agent having a macrophage-foaming reaction suppressing effect and a method for treating hyperlipidemia and arteriosclerosis using this composition.

[0002] As people have become more affluent, their eating habits have changed toward increased intake of foods with high cholesterol content and high caloric value. As a result, hyperlipidemia and arteriosclerosis are increasing rapidly in conjunction with the aging of the population. This has become a major social problem.

[0003] Hitherto, drug therapy for hyperlipidemia and arteriosclerosis has been directed only to lowering blood cholesterol. No drug capable of reversing the effects of arteriosclerosis is available.

[0004] Arteriosclerosis is characterized by thickening of the blood vessel intima and lipid deposition within the blood vessel. Therefore, for drug therapy of the disease, drugs capable of lowering blood cholesterol have been used. However, it has been found that the macrophage-foaming reaction plays an important role in forming the focus of arteriosclerosis. Thus, it is expected that suppression of this reaction would result in regression of the arteriosclerosis foci. AM. J. Path. 1991, 139, pp. 217-229 discloses that various lipid-regulating agents induce hepatomegaly, heptatic peroxisome proliferation, and hepatocarcinoma in rats. One such compound is



Summary of the Invention

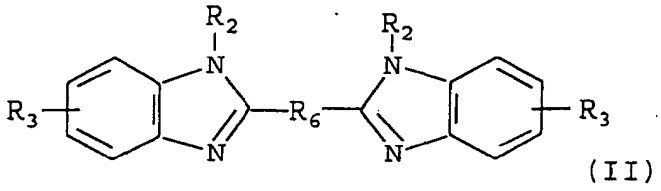
[0005] A primary object of the present invention is to provide a novel and low toxic pharmaceutical composition capable of lowering blood cholesterol and suppressing macrophage-foaming reaction by way of inhibiting acyl-CoA cholesterolacyltransferase (ACAT) activity and intracellular cholesterol transport.

[0006] Another object of the present invention is to provide the use of certain compounds for the manufacture of medicaments for treating hyperlipidemia and arterisclerosis.

[0007] These and other objects of the present invention will be apparent from the following description and Examples.

[0008] The above objects were achieved based on the discovery that certain benzimidazole and 2,2'-methylenebisphenol derivatives have not only an ACAT activity-inhibiting effect, an intracellular cholesterol transport-inhibiting effect and an excellent blood cholesterol lowering effect but also a macrophage-foaming reaction suppressing effect, and, as such, are able to achieve the aforesaid object.

[0009] According to a first aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (II) or (III), or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent:



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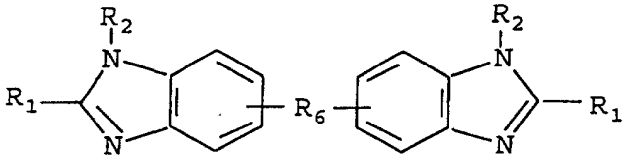


(III)

wherein

R_1 represents a hydrogen atom, an alkyl, an aryl, a mercapto, an alkylthio, and alkenylthio, an arylthio or a heterocyclo group;

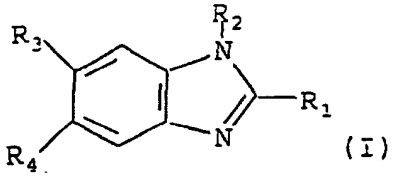
R_2 represents a hydrogen atom or an alkyl group, provided that the alkyl group is not substituted by a hydroxyl group;

R_3 represents a hydrogen atom, a halogen atom, a nitro group, R_5O-, R_5CONH-, R_5NHCO-, $(R_5)_2NCO$-, R_5SO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- or $R_5NHCONH$- where R_5 represents an alkyl or an aryl group; and

R_6 represents a divalent group.

[0010] According to a second aspect, the present invention provides the use of the compounds of the formula (II) or (III), or a pharmaceutically-acceptable salt thereof, as defined above, for the manufacture of a pharmaceutical composition for treating hyperlipidemia and arteriosclerosis in a mammal, preferably man.

[0011] According to a third aspect, the present invention provides the use of a compound of formula (I):



(I)

wherein

R_1 represents a hydrogen atom, an alkyl, a mercapto, an alkylthio, an alkenylthio, an arylthio or a heterocyclo group;

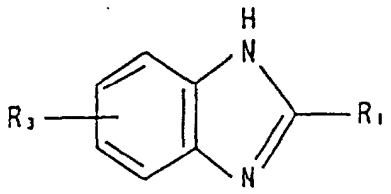
R_2 represents a hydrogen atom or an alkyl group optionally substituted by an aryl, an amino or an acylamino group; and

R_3 and R_4 each independently represents a hydrogen atom, a halogen atom, a nitro group, R_5O-, R_5CONH-, R_5NHCO-, $(R_5)_2NCO$-, R_5SO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- or $R_5NHCONH$- where R_5 represents an alkyl or an aryl group, for the manufacture of a pharmaceutical composition for treating hyperlipidemia and arteriosclerosis in mammals, preferably man.

Detailed explanation of preferred Embodiments

[0012] The present invention provides a pharmaceutical composition which has an excellent blood cholesterol lowering effect and macrophage-foaming reaction suppressing effect and is low in toxicity, it therefore exhibits an excellent therapeutic effect on hyperlipidemia and arteriosclerosis and is administrable over a long period.

[0013] Among the compounds of the formulae (I), (II) and (III), the compounds of the formula (I) are preferable and, in the compounds of the formula (I), the compounds of the following formula (V) are particularly preferable;



(V)

wherein

R_1 represents a hydrogen atom, an alkyl, a mercapto or an alkylthio group; and

R_3 represents a hydrogen atom, a halogen atom, a nitro group, R_5O-, R_5CONH-, R_5NHCO-, R_5NHSO_2- or R_5SO_2NH- where R_5 represents an alkyl group.

[0014] The compounds of the formulae (I), (II), (III) and (V) of the present invention will now be described in detail.

[0015] Examples of the alkyl groups represented by R_1 in the formulae (I), (III) and (V) include alkyl groups having 1 to 18 carbon atoms (such as methyl, ethyl, butyl, octyl, dodecyl and octadecyl groups). Alkyl groups having 1 to 8 carbon atoms (such as methyl, ethyl, butyl and octyl groups), which may be straight or branched chains, are preferable. Examples of the alkyl groups of the alkylthio groups include alkyl groups having 1 to 18 carbon atoms (such as methyl, ethyl, butyl, octyl, dodecyl and octadecyl groups). Alkyl groups having 1 to 8 carbon atoms (such as methyl, ethyl, butyl and octyl groups), which may be straight or branched chains, are preferable. Examples of the alkenyl groups of the alkenylthio groups include alkenyl groups having 2 to 18 carbon atoms (such as allyl and octadecenyl groups). Examples of the aryl groups of the arylthio groups include phenyl and naphthyl groups. Phenyl group is particularly preferable. Examples of the heterocyclo groups of the heterocyclothio groups include pyridyl and hexahydropyridyl groups. 2-and 4-pyridyl groups are particularly preferable.

[0016] Each of the alkyl, alkylthio, alkenylthio, arylthio and heterocyclothio groups represented by R_1 may be optionally substituted. Examples of the substituents include halogen atoms, alkyl, aryl, alkoxy, aryloxy, acylamino and nitro groups.

[0017] Preferred groups represented by R_1 are hydrogen atom, alkyl groups, mercapto group and alkylthio groups. Specific examples of the preferred groups represented by R_1 include methyl, butyl, mercapto and methylthio groups.

[0018] Next, examples of the alkyl groups represented by R_2 in the formulae (I) to (III) include alkyl groups having 1 to 12 carbon atoms (such as methyl, butyl, hexyl, octyl and dodecyl groups). Alkyl groups having 1 to 6 carbon atoms (such as methyl, butyl and hexyl groups), which may be straight or branched chains, are preferable.

[0019] The alkyl group represented by R_2 is optionally substituted by aryl, amino or acylamino groups. The alkyl group is not substituted by hydroxy group.

[0020] Preferred groups represented by R_2 are hydrogen atom and the alkyl groups having 1 to 6 carbon atoms, particularly hydrogen atom.

[0021] When R_3 in the formulae (I), (II) and (V) and R_4 in the formula (I) contain R_5, examples of the alkyl groups represented by R_5 include alkyl groups having 1 to 20 carbon atoms (such as methyl, butyl, octyl, dodecyl and octadecyl groups). Alkyl groups having 4 to 18 carbon atoms (such as methyl, butyl, octyl, dodecyl and octadecyl groups), which may be straight or branched chains, are preferable. Examples of the aryl groups include phenyl and naphthyl groups. Phenyl group is particularly preferable.

[0022] The alkyl and aryl groups represented by R_5 may be optionally substituted. Examples of the substituents include halogen atoms, alkyl, aryl, acylamino and aryloxy groups.

[0023] Preferred groups represented by R_3 and R_4 are the above-described groups containing R_5, that is, R_5O-, R_5CONH-, R_5NHCO-, R_5SO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- and $R_5NHCONH$-, particularly R_5O-, R_5CONH-, R_5NHCO-, R_5NHSO_2- and R_5SO_2NH-. Specific examples of the preferred groups include octyloxy, hexadecyloxy, dodecanoyloxy, dodecylcarbamoyl, octylsulfonylamino, dodecylsulfamoyl groups.

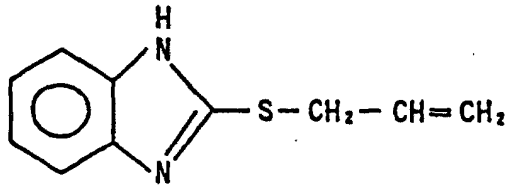
[0024] Examples of the divalent groups represented by R_6 in the formulae (II) and (III) include $-(CH_2)_n-$, -, $-O(CH_2)_nO-$, O-, $-NHCO(CH_2)_n$ CONH-, $-NHSO_2(CH_2)_n$ SO_2NH- where n represents an integer of 1 to 10.

[0025] $-(CH_2)_n$ - and $-NHCO(CH_2)_n$ CONH- where n is 2 to 8 are particularly preferable.

[0026] Among the above-described compounds having R_1 to R_6, preferred are the compounds in which at least one substituents have not less than 4 carbon atoms, particularly those in which at least one substituents except for R_2 have 4 to 20 carbon atoms, preferably 8 to 18 carbon atoms.

[0027] Examples of the parmaceutically-acceptable salts of the compounds represented by the formulae (I), (II) and (III) include hydrochloride, hydrobromide, nitrate, sulfate and toluenesulfonate. Hydrochloride is particularly preferable.

[0028] Examples of the compounds of the formulae (I), (II) and (III) or the formula (V) of the present invention are listed below.



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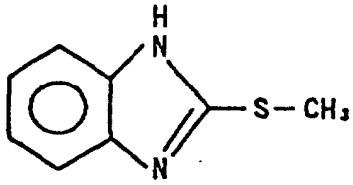

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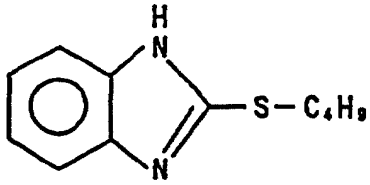

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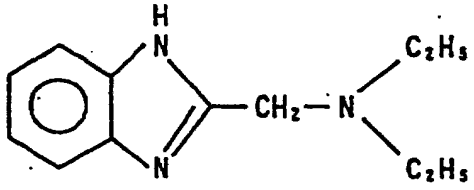

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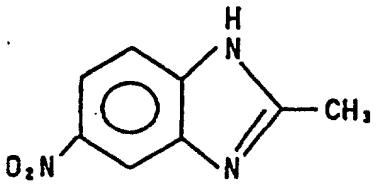

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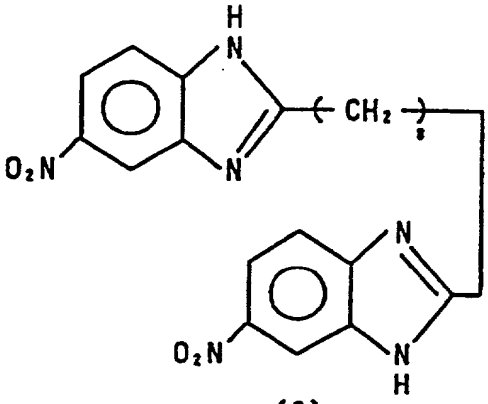

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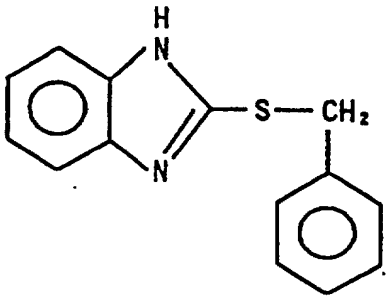

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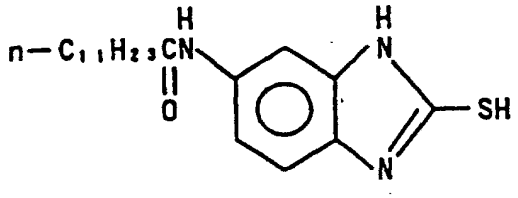

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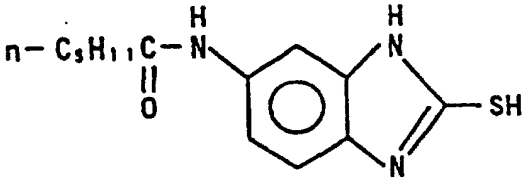

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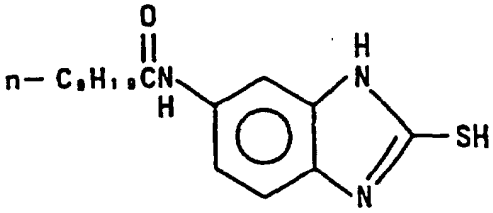

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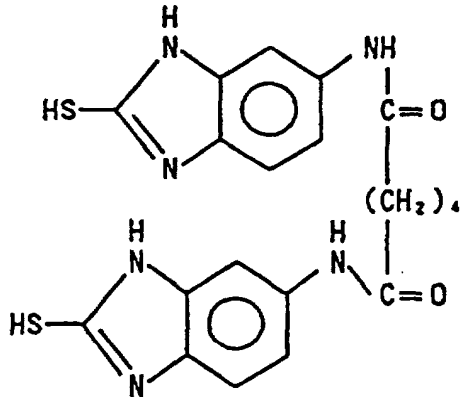

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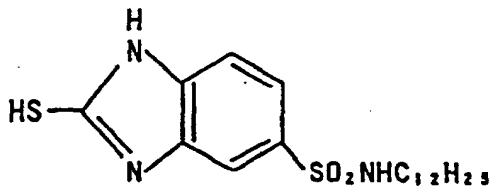

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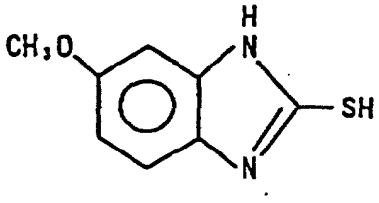

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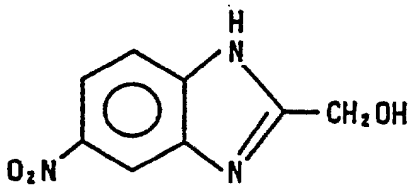

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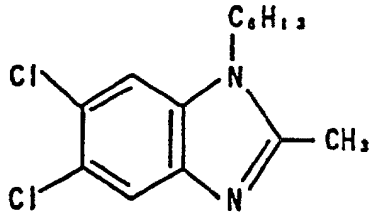

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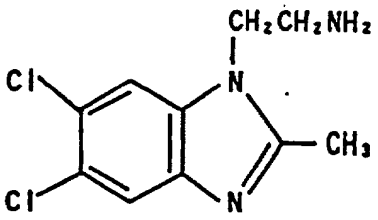

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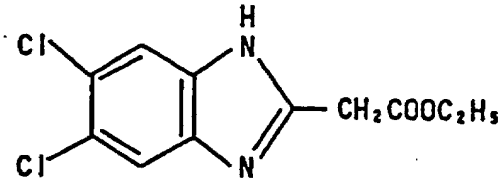

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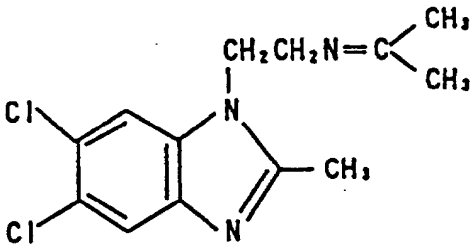

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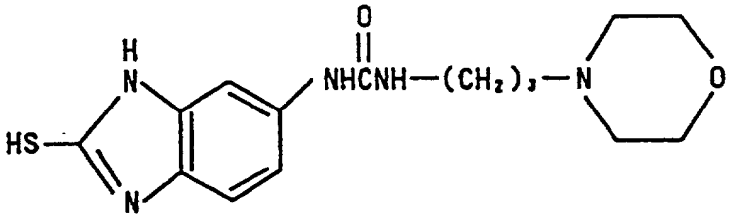

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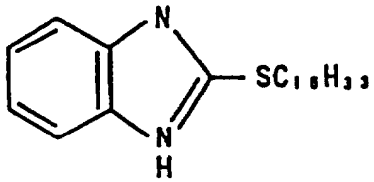

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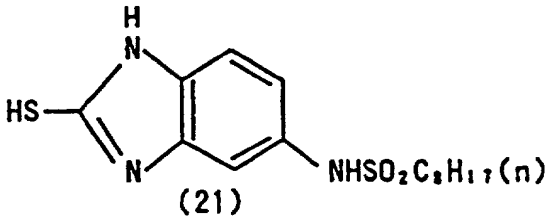

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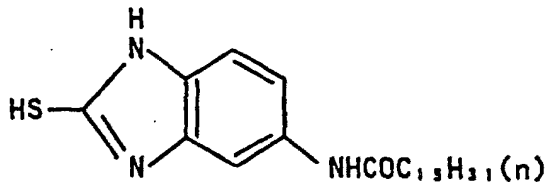

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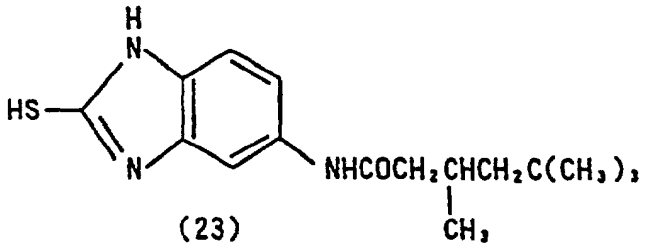

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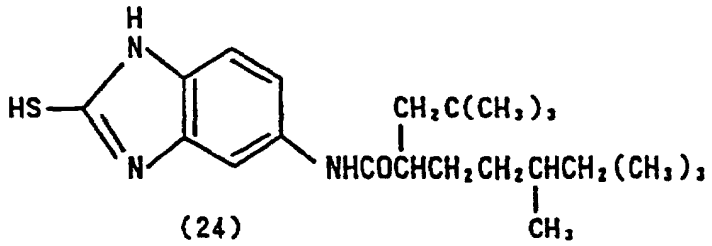

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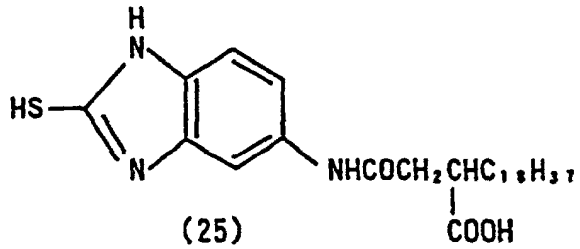

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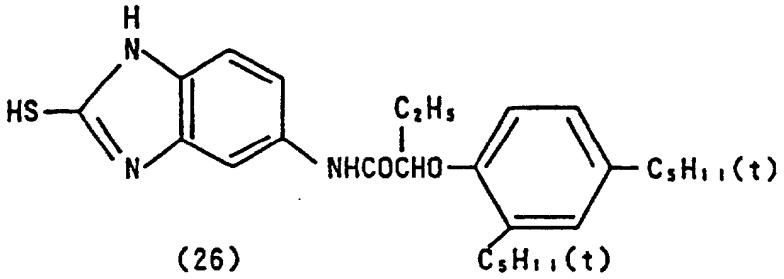

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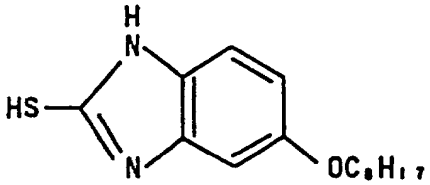

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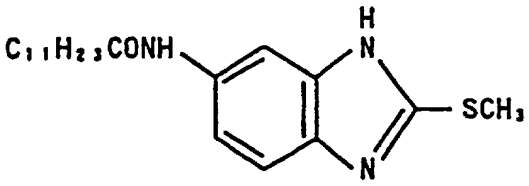

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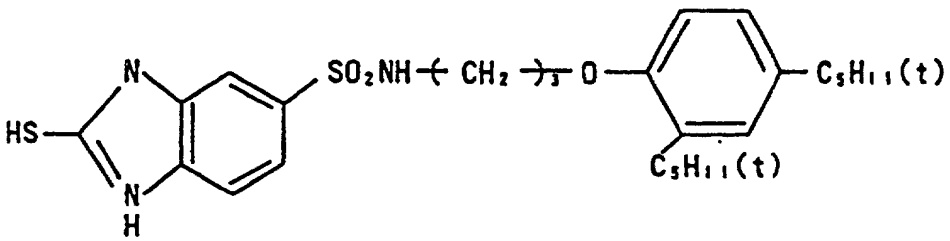

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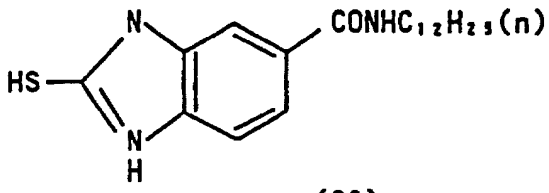

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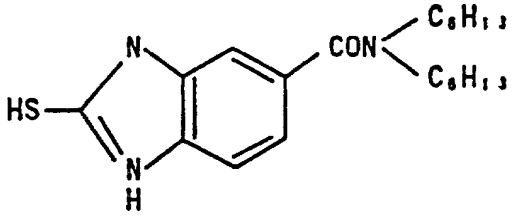

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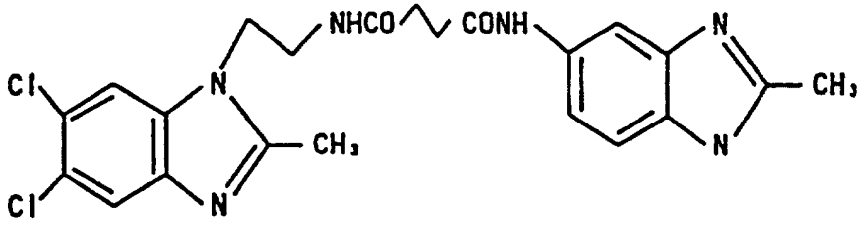

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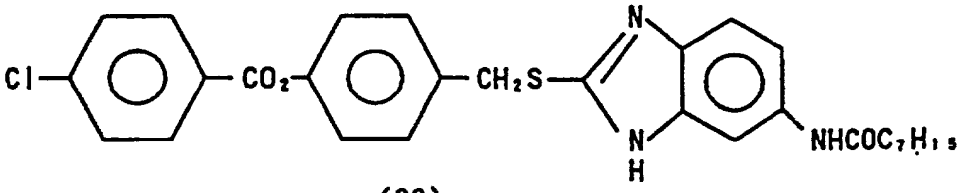

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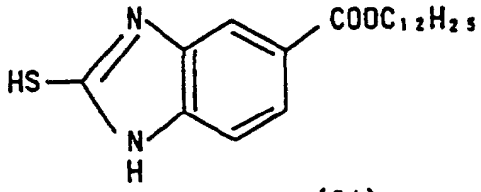

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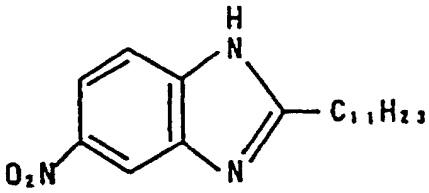

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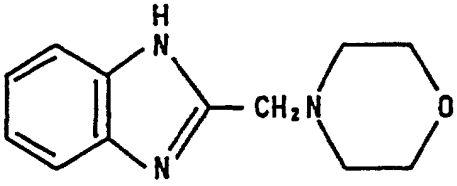

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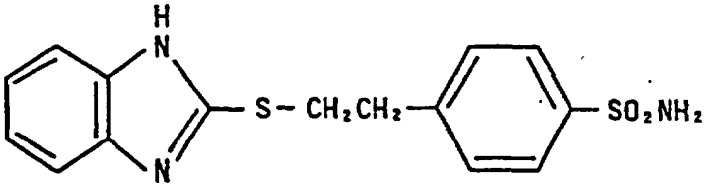

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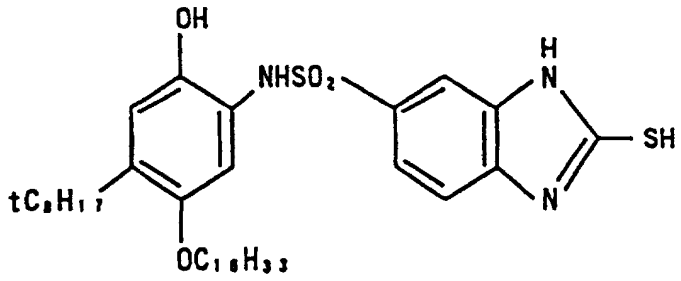

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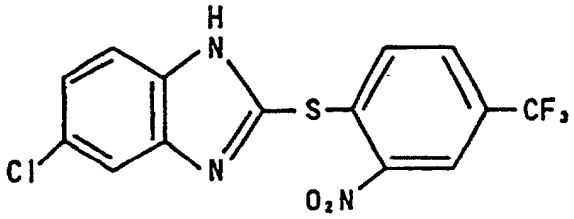

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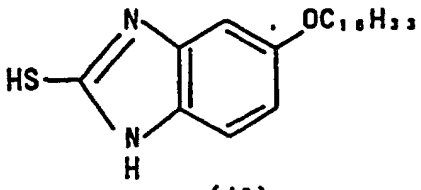

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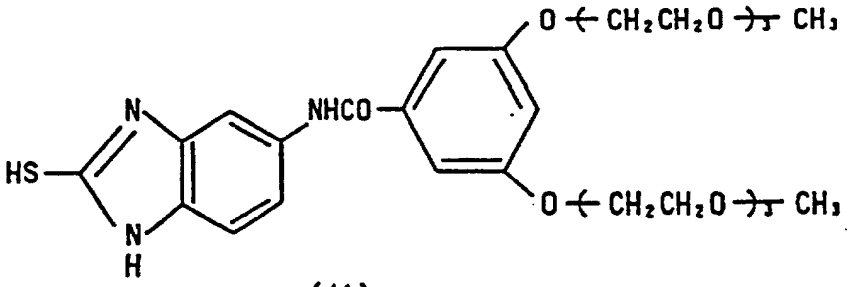

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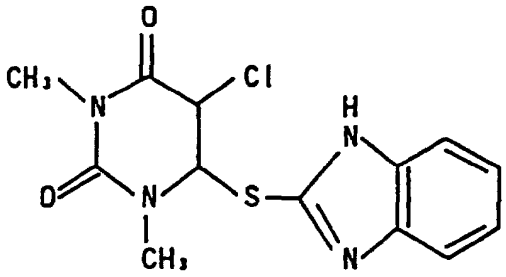

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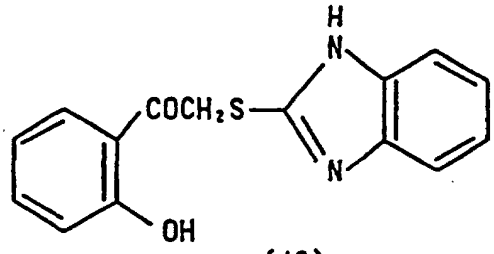

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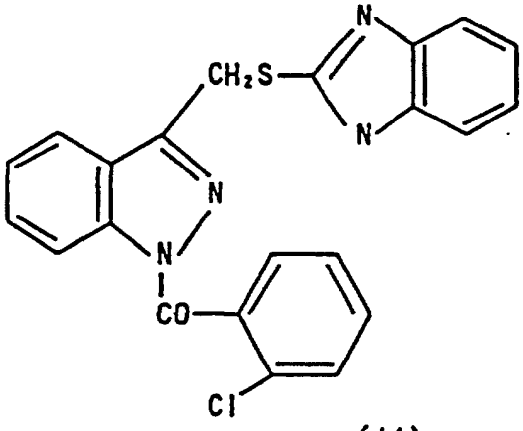

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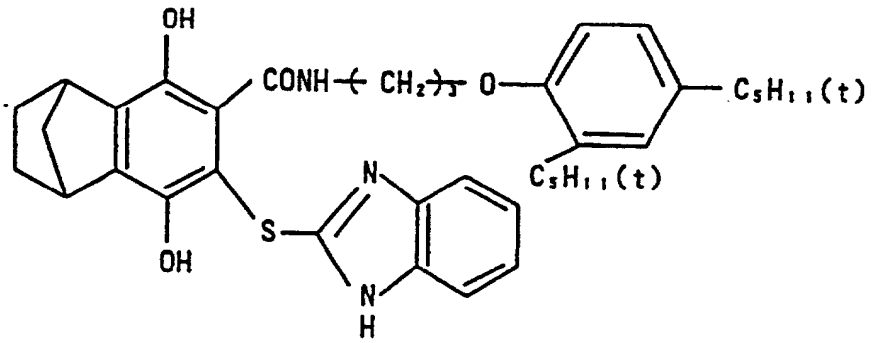

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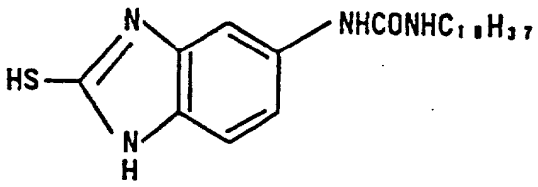

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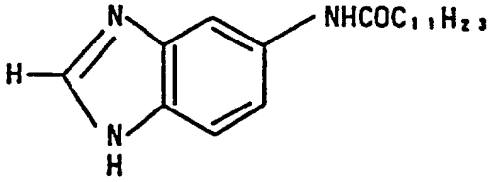

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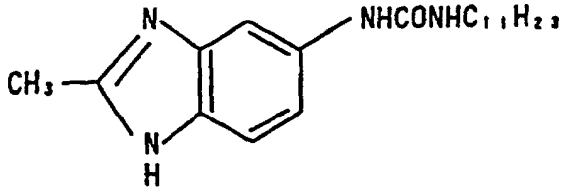

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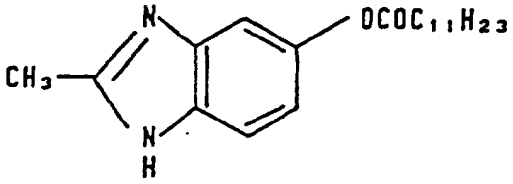

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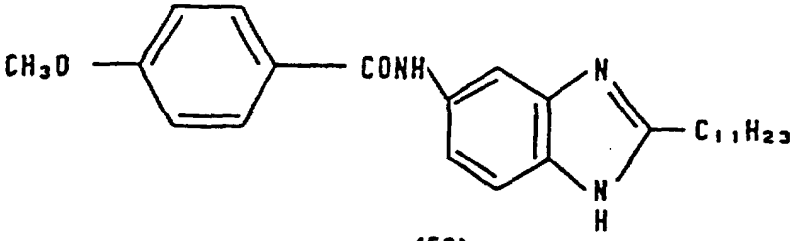

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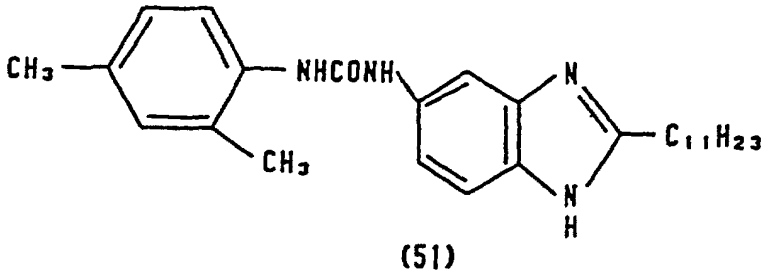

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[0029] The method for preparing these compounds will now be described in detail.

[0030] Benzimidazole ring which is basic skeleton of the compounds of the formulae (I), (II) and (III) is generally synthesized using a o-phenylenediamine as a starting material. That is 2-mercaptobenzimidazoles are generally synthesized by reacting o-phenylenediamines with carbon disulfide under a basic condition and 2-alkyl- or 2-aryl benzimidazoles are generally synthesized by reacting o-phenylenediamines with carboxylate or orthocarboxylate under an acidic condition.

Synthesis Example 1 Synthesis of 2-metyl-5-nitrobenzimidazole (5)

[0031] 15.3 g of 3,4-dinitrobenzene was added to 64 ml of acetic anhydride and 2 ml of conc. hydrochloric acid and the mixture was refluxed for 3 hours. After cooling, the formed crystals were dispersed in 10 % sodium hydroxide aqueous solution and then filtered off. The crystals were recrystallized from water-containing ethanol to obtain 6 g of compound (5).

Melting point	220-221 °C			
Elemental analysis (%)	Anal.	C 54.42	H 4.03	N 23.62
	Cal.	C 54.23	H 3.98	N 23.72

Synthesis Example 2 Synthesis of 1,8-bis(5-nitrobenzimidazol-2-yl) octane (6)

[0032] 10.8 g of o-phenylenediamine and 10.1 g of sebacic acid were added to 120 ml of 4 N hydrochloric acid and the mixture was refluxed for 6 hours. After cooling, the formed crystals were filtered off and washed with 1 N sodium carbonate aqueous solution until the washing solution maitained an alkalinity. After separating and drying the crystals, they were dissolved in 35 ml of conc. sulfuric acid and 3.8 g of potassium nitrate was added thereto little by little while stirring under cooling with ice. After stirring for 2 hours under cooling with ice, the solution was poured into ice-water and the formed crystals were washed with 1 N sodium carbonate aqueous solution until the washing solution maitained an alkalinity. The crystals were recrystallized from water-containing ethanol to obtain 3.4 g of compound (6).

Melting point	135-137 °C			
Elemental analysis (%)	Anal.	C 60.62	H 19.25	N 5.41
	Cal.	C 60.54	H 19.26	N 5.54

Synthesis Example 3 Synthesis of 2-mercapto-5-methoxybenzimidazole(13)

[0033] 70 ml of ethanol and 15 ml of carbon disulfide were added to 2.6 g of 3,4-diaminoanisole and then a solution of 1.5 g of sodium hydroxide in 5 ml of water was added thereto. After heating with a water bath for 3.5 hours, the mixture was cooled with ice, filtered and then the solvent in the filtrate was distilled off under reduced pressure. The residue was dissolved in ethanol. The solution was filtrated to remove the insoluble matter and then the solvent in the filtrate was distilled off under reduced pressure. The residue was recrystallized from water-containing methanol to obtain 2.0 g of the titled compound (13).

Melting point	254-255 °C			
Elemental analysis (%)	Anal.	C 53.06	H 4.52	N 15.27
	Cal.	C 53.33	H 4.44	N 15.56

Synthesis Example 4 Synthesis of 2-benzylthiobenzimidazole (7)

[0034] 15 g of 2-mercaptobenzimidazole and 16.5 g of benzylbromide were dissolved in 50 ml of ethanol and the mixture was refluxed with a water bath for 5 hours. After cooling, the formed crystals were collected and recrystallized from ethanol to obtain 18 g of compound (7).

Melting point	185-186 °C			
Elemental analysis (%)	Anal.	C 69.59	H 5.30	N 11.74
	Cal.	C 69.99	H 5.03	N 11.66

Synthesis Example 5 Synthesis of 5-dodecanoylamino-2-mercaptobenzimidazole (8)

[0035] 5 g of 5-amino-2-mercaptobenzimidazole was dissolved in 50 ml of pyridine and 7.95 g of dodecanoyl chloride was added dropwise thereto under cooling with ice. After stirring for 3 hours at room temperature, the solution was poured into ice-water. The formed crystals were filtered off and recrystallized from water-containing methanol to obtain 10.9 g of compound (8).

Melting point	266-267 °C			
Elemental analysis (%)	Anal.	C 66.38	H 8.54	N 11.34
	Cal.	C 65.71	H 8.36	N 12.10

Synthesis Example 6 Synthesis of 2-morpholinomethylbenzimidazole (36)

[0036] To 108 g of o-phenylenediamine, 1 ℓ of 4 N hydrochloric acid and 142 g of chloroacetic acid were added and refluxed for 1.5 hours. After allowing to stand overnight, the solution was diluted with 2 ℓ of water and neutralized with dilute ammonia water. The formed crystals were filtered off to obtain 113 g of 2-chlorom ethylbenzimidazole.

[0037] 10 g of 2-chloromethylbenzimidazole thus obtained and 10.5 g of morpholine were dissolved in 75 ml of alcohol and the solution was refluxed for 3 hours. After cooling, ether was added to the solution and the precipitated crystals were filtered off. The filtrate was washed with water and satulated with hydrogen chloride to form an oily matter. The oily matter was crystallized by adding a smoll amount of alcohol and the crystals were filtered off. The crystals were recrystallized from alcohol to obtain 2.5 g of compound (36).

Melting point	235-236 °C			
Elemental analysis (%)	Anal.	C 49.48	H 5.88	N 14.27
	Cal.	C 49.66	H 5.91	N 14.48

[0038] The following compounds were synthesized according to the method above described. The melting points of the crystalline compounds are as follows:

Compound No.	m.p.(°C)	Compound No.	m.p.(°C)
(1)	195-200 (HCl salt)	(2)	200-203
(3)	133-135 (HBr salt)	(4)	167-170
(5)	220-221	(6)	135-137
(7)	190-191	(8)	226-267
(9)	266-268	(10)	275-276
(11)	>300	(12)	>280
(13)	254-255	(14)	128-129
(15)	95-97	(16)	106-108

(continued)

Compound No.	m.p.(°C)	Compound No.	m.p.(°C)
(17)	181-183	(18)	119-123
(20)	84-87	(21)	183-186
(23)	250-252	(24)	214-217
(25)	200 (decomp.)	(26)	284-286
(27)	230-232	(28)	132-134
(29)	217 (decomp.)	(30)	243-245
(31)	143-144	(32)	>250
(33)	124-125	(34)	218-220
(35)	215-217 (HCl salt)	(36)	235 (decomp.) (HCl salt)
(37)	162-164	(38)	215-216
(39)	202-203	(42)	230-231
(43)	155-156	(44)	163-164
(45)	146 (decomp.)	(46)	197-199
(47)	54-56	(48)	60-63
(49)	82-85	(50)	188-191
(51)	209-212		

[0039] The pharmaceutical composition of the present invention may contain one or more compounds of formulae (II) to (III) and may be used in combination with the known antihyperlipidemia and antiarteriosclerosis agents that are conventionally used and are compatible with the compounds of the present invention. Examples of known antihyperlipidemia and antiarteriosclerosis agents include Melinamide, Probucol and Mevalotin.

[0040] The pharmaceutical composition of the present invention may be administered, for example, orally or by injection (mainly intramuscular, intravenous or subcutaneous route) and is usually prepared in the form of a formulation suitable for the administration route. Thus, the pharmaceutical composition can be used as an oral formulation such as tablet, powder, granule, capsule, syrup, emulsion, suspension or solution, or injection. The formulations can be prepared by mixing the compound of the present invention with a pahrmaceutical-acceptable carrier, diluent and/or bioactive substance.

[0041] Examples of pharmaceutical carriers or diluents suitable for combining with the compound of formula (I) to (III) include glucose; saccharose; lactose; ethanol; glycerin; mannitol; sorbitol; pentaerythritol; diethylene glycol, triethylene glycol, ethylene glycol, propylene glycol, dipropylene glycol, polyethylene glycol 400, other polyethylene glycols than polyethylene glycol 400; mono-, di- and triglycerides of saturated fatty acids such as trilauryl glyceride, monostearoyl glyceride, tristearoyl glyceride and distearoyl glyceride; pectin; starch; corn starch; arginic acid; xylose; talc, lycopodium; oils and fats such as olive oil, peanut oil, castor oil, corn oil, wheat malt oil, sesame oil, cottonseed oil, sunflower oil and cod-liver oil; gelatin; lecithin; silica; cellulose; cellulose derivatives such as hydroxypropyl methyl cellulose, methylcellulose, hydroxyethyl cellulose and calcium carboxymethyl cellulose; magnesium or calcium salts of fatty acids having 12 to 22 carbon atoms such as calcium stearate, calcium laurate, magnesium oleate, calcium palmitate, calcium behenate and magnesium stearate; cyclodextrins such as α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, dihydroxypropyl-β-cyclodextrin, carboxymethyl ethyl-β-cyclodextrin and dimethyl-β-cyclodextrin; emulsifiers such as esters of saturated and unsaturated fatty acids having 2 to 22, particularly 10 to 18 carbon atoms, with monovalent aliphatic alcohols (for example, alkanols having 1 to 20 carbon atoms such as glycol, glycerin, diethylene glycol, pentaerythritol, ethanol, butanol and octadecanol) or polyvalent alcohols; silicones such as dimethyl polysiloxane; and pyrogen-free distilled water.

[0042] The dosage of the pharmaceutical composition of the present invention varies depending on age, body weight, severity of the disease of the patient and the administration route. However, in general, the quantity of the compound of formula (I), (II) and/or (III) to be administered ranges from 0.1 to 500 mg, preferably from 0.2 to 100 mg per day per kg of body weight for adult.

Pharmaceutical test

(1) In vitro test for suppressing effect of macrophage-foaming reaction using mouse abdominal cavity macrophage

[0043] A 15-week old ICR female mouse (Japan SLC) was amputated at its neck and exsanguinated. Then, Hanks

buffer (Nissui Pharmaceutical Co., Ltd.) was injected intraperitoneally. After massaging the abdominal part, the buffer was recovered rapidly and centrifuged at 1,000 rpm for 5 minutes to collect the abdominal cavity macrophage. Then, the collected abdominal cavity macrophage was suspended in GIT medium (Wako Pure Chemical Industry) and inoculated on a 24-well microplate. After culturing the macrophage for 2 hours at 37 °C in 5 % CO_2, the medium was changed into Dulbecco modified Eagle's MEM medium (Nissui Pharmaceutical Co., Ltd.). After further culturing the macrophage for 16 hours at 37 °C in 5 % CO_2, the following substances were added in order:

① Test compounds: solutions in DMSO (Wako Pure Chemical Industry) 1 ml of the solutions were prepared, optionally diluted and the diluted solutions were added to individual wells (500 μℓ) in the amount of 5 μℓ.
② Liposome
PC/PS/DCP/CHOL. 50/50/10/75 (nmol)
PC : phosphatidylcholine (Funakoshi)
PS : phosphatidylserine (Funakoshi)
DCP : dicetylphosphate (Funakoshi)
CHOL. : cholesterol (Sigma)
③ ^{3}H-Oleic acid (Amersham Japan)

[0044] Then, after still further culturing the macrophage for 16 hours at 37 °C in 5 % CO_2, the lipid fraction was extracted with chloroform and methanol. The extracted lipid fraction was subjected to TLC (hexane:ether:acetic acid = 70:30:1), the separated bands of CE (cholesteryl ester) and TG (triglyceride) were borne off from the TLC plate and then the radioactivities thereof were measured using a liquid scintillation counter (PACKARD BH-22). Yields of cholesteryl ester were calculated by comparing with a control. The results are shown in Table 1.

Table 1

Compound No.	Dosage	Yield of CE (%)	Yield of TG (%)
(3)	5 μM	69	89
(5)	5 μM	67	89
(6)	5 μM	8.0	61
(7)	5 μM	61	91
(8)	5 μM	42	106
(10)	5 μM	69	129
(12)	5 μM	52	102
(20)	5 μM	49	62
(21)	5 μM	64	93
(23)	5 μM	56	119
(27)	5 μM	51	78
(28)	5 μM	53	164
(30)	5 μM	51	91
(34)	5 μM	50	108
(42)	5 μM	61	96
(43)	5 μM	45	98
(47)	5 μM	55	98

[0045] It is clear from Table 1 that these compounds do not lower the yield of TG so far, that is, these compounds are low toxic and capable of markedly suppressing the yield of CE. Namely, these compounds markedly suppress the macrophage-foaming reaction without being highly toxic to the macrophage.

(2) Blood lipid lowering effect in rabbit fed high-cholesterol feed

[0046] (i) New Zealand White female rabbits having body weight of about 2 kg were fed feed having high cholesterol content (100g/day/rabbit: ORC-4 manufactured by Oriental Yeast, containing 0.5 % of cholesterol and 0.5 % of olive oil) for 7 days to produce hypercholesterolemia.

[0047] Subsequently, one group consisting of 3 rabbits (treatment group) was fed the same feed in the same amount, except that the feed further contained test compound (8) in the amount of 10 0mg/kg/day/rabbit, for 7 successive days. On the other hand, as a control, another group consisting of 3 rabbits was fed the same feed in the same amount

without any test compound.

[0048] A small amount of blood was drawn from the parotic vein of every rabbit once a week and was measured for amount of blood total cholesterol using IATROLIPO TC manufactured by Iatron Laboratories Inc.

[0049] The amount of blood total cholesterol of the treatment group fell by 25 % in comparison with the control group (3 rabbits).

[0050] Thus, it is clear that test compound (8) has an excellent lowering effect of the blood cholesterol.

(3) Blood lipid lowering effect in rabbit fed normal feed

[0051] (i) New Zealand White female rabbits having body weight of about 2 kg were fed normal feed (100g/day/rabbit: ORC-4 manufactured by Oriental Yeast) for 7 days.

[0052] Subsequently, one group consisting of 3 rabbits (treatment group) was fed the normal feed in the same amount, except that the feed further contained test compound (2) in the amount of 10 0mg/kg/day/rabbit, for 7 successive days. As a control, another group consisting of 3 rabbits was fed the normal feed in the same amount without any test compound.

[0053] A small amount of blood was drawn from the parotic vein of every rabbit once a week and was measured for amount of blood total cholesterol using IATROLIPO TC manufactured by Iatron Laboratories Inc.

[0054] The amount of blood total cholesterol of the treatment group fell by 20 % in comparison with the control group' (3 rabbits).

[0055] Thus, it is clear that test compound (2) has an excellent blood cholesterol lowering effect not only on rabbits fed high-cholesterol feed but also on rabbits fed normal feed.

(4) Acute toxicity test

[0056] Compound (2) was suspended in 0.5 % Tween 80 solution. Six 8-week old ddy mice were orally administered the suspension and were observed on acute toxicity. As a result, the LD50 value of the compounds of the present invention were found to be not less than 1000 mg/kg. This value indicates that the compounds of the present invention is low in toxicity.

Examples

Example 1 Tablet

[0057] Preparation of tablet containing 25 mg of compound (8)

①	compound (8)	10 g
②	corn starch	40 g
③	crystalline cellulose	45 g
④	calcium carboxylmethyl cellulose	4 g
⑤	light silicic acid anhydride	500 mg
⑥	magnesium stearate	500 mg
Total		100 g

[0058] ① to ⑤ were homogeneously mixed and the resulting mixture was compression molded with a tableting machine to obtain tablets having weight of 250 mg. Each of these tablets contained 25 mg of compound (8). An adult may take 5 to 30 tablets over the course of one day.

Example 2 Capsule

[0059] Preparation of capsule containing 40 mg of compound (8)

①	compound (8)	20 g
②	corn starch	79.5 g
③	light silicic acid anhydride	500 mg
Total		100 g

[0060] ① to ③ were homogeneously mixed and the resulting mixture was encapsulated in the amount of 200 mg per capsule. Each of thus-obtained capsules contained 40 mg of compound (8). An adult may take 1 to 20 capsules over the course of one day.

Example 3 Granule

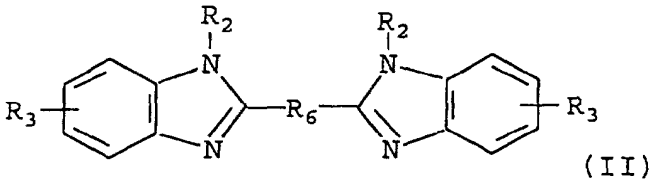
[0061] Preparation of granule containing 100 mg of compound (8) per 1 g

①	compound (8)	10 g
②	corn starch	40 g
③	10% hydroxypropyl cellulose solution in ethanol	50 g
Total		100 g

[0062] ① to ③ were homogeneously mixed. After kneading, the mixture was granulated with a granulating machine and dried to obtain granules. These capsules contained 100 mg of compound (8) per 1 g. An adult may take 1 to 8 g over the course of one day.

Claims

1. A pharmaceutical composition comprising a compound of formula (II) or (III), or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically-acceptable carrier or diluent:



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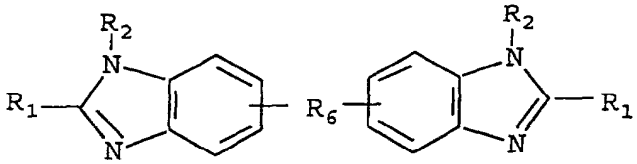


(III)

wherein

R_1 represents a hydrogen atom, an alkyl, an aryl, a mercapto, an alkylthio, and alkenylthio, an arylthio or a heterocyclo group;

R_2 represents a hydrogen atom or an alkyl group, provided that the alkyl group is not substituted by a hydroxyl group;

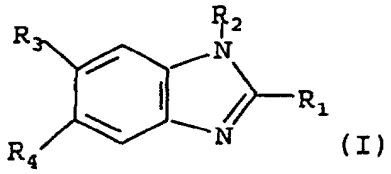
R_3 represents a hydrogen atom, a halogen atom, a nitro group, R_5O-, R_5CONH-, R_5NHCO-, $(R_5)_2NCO$-, R_5SO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- or $R_5NHCONH$- where R_5 represents an alkyl or an aryl group; and

R_6 represents a divalent group.

2. The use of a compound of the formula (II) or (III), or a pharmaceutically-acceptable salt thereof, as defined in Claim 1, for the manufacture of a pharmaceutical composition for treating hyperlipidemia and arteriosclerosis in mammals,

preferably man.

3. The use of a compound of formula (I):



(I)

wherein

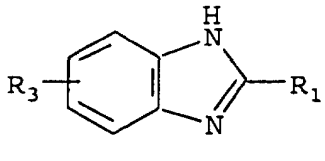
R_1 represents a hydrogen atom, an alkyl, a mercapto, an alkylthio, an alkenylthio, an arylthio or a heterocyclo group;

R_2 represents a hydrogen atom or an alkyl group optionally substituted by an aryl, an amino or an acylamino group; and provided that the alkyl group is not substituted by a hydroxyl group;

and R_3 and R_4 each independently represents a hydrogen atom, a halogen atom, a nitro group, R_5O-, R_5CONH-, R_5NHCO-, $(R_5)_2NCO$-, R_5SO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- or $R_5NHCONH$- where R_5 represents an alkyl or an aryl group,

for the manufacture of a pharmaceutical composition for treating hyperlipidemia and arteriosclerosis in mammals, preferably man.

4. The use according to Claim 3, wherein the compound of the formula (I) is represented by the following formula (V);



(V)

wherein

R_1 represents a hydrogen atom, an alkyl, a mercapto or an alkylthio group; and

R_3 represents a hydrogen atom, a halogen atom, a nitro group, R_5O-, R_5CONH-, R_5NHCO-, R_5NHSO_2- or R_5SO_2NH- where R_5 represents an alkyl group.

5. The use according to Claim 4, wherein R_1 represents a hydrogen atom, an alkyl group having 1 to 18 carbon atoms, a mercapto group or an alkylthio group having 1 to 18 carbon atoms; and

R_5 represents an alkyl group having 1 to 20 carbon atoms.

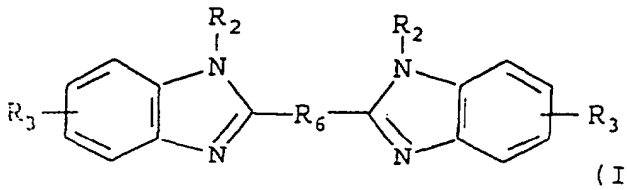
6. The use according to Claim 5, wherein

R_1 represents a hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a mercapto group or an alkylthio group having 1 to 8 carbon atoms; and

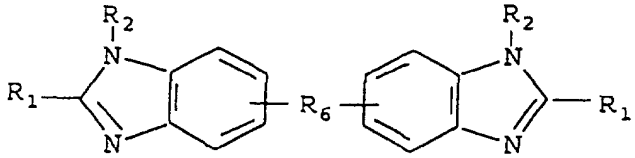
R_5 represents an alkyl group having 4 to 18 carbon atoms.

Patentansprüche

1. Pharmazeutische Zusammensetzung enthaltend eine Verbindung der Formel (II) oder (III) oder ein pharmazeutisch annehmbares Salz davon zusammen mit einem pharmazeutisch annehmbaren Träger oder Verdünner:



(II)



(III)

worin

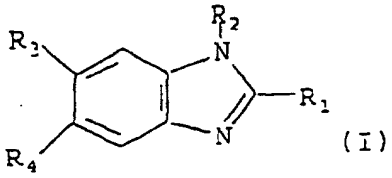
R_1 ein Wasserstoffatom, eine Alkyl-, eine Aryl-, eine Mercapto-, eine Alkylthio-, eine Alkenylthio-, eine Arylthio- oder eine Heterocyclo-Gruppe darstellt;

R_2 stellt dar ein Wasserstoffatom oder eine Alkyl-Gruppe, vorausgesetzt, daß die Alkyl-Gruppe nicht mit einer Hydroxyl-Gruppe substituiert ist;

R_3 stellt dar ein Wasserstoffatom, ein Halogenatom, eine Nitro-Gruppe, R_5O-, R_5CONH-, R_5NHCO-, $(R_5)_2NCO$-, R_5SO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- oder $R_5NHCONH$-, worin
R_5 eine Alkyl- oder eine Aryl-Gruppe darstellt und
R_6 stellt eine zweiwertige Gruppe dar.

2. Die Verwendung einer Verbindung der Formel (II) oder (III) oder eines pharmazeutisch annehmbaren Salzes davon, gemäß Anspruch 1, zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung von Hyperlipidämie oder Arteriosklerose in Säugetieren bevorzugt Mensch.

3. Verwendung einer Verbindung gemäß Formel (I):



(I)

worin

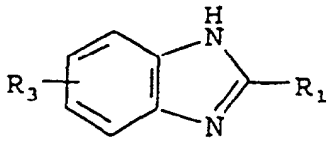
R_1 ein Wasserstoffatom, eine Alkyl-, eine Mercapto-, eine Alkylthio-, eine Alkenylthio-, eine Arylthio- oder Heterocyclo-Gruppe darstellt;

R_2 stellt dar ein Wasserstoffatom oder eine Alkyl-Gruppe, gegebenenfalls substituiert mit einer Aryl-, eine Amino- oder einer Acylamino-Gruppe und vorausgesetzt, daß die Alkyl-Gruppe nicht mit einer Hydroxyl-Gruppe substituiert ist, und

R_3 und R_4 stellen unabhängig dar ein Wasserstoffatom, ein Halogenatom, eine Nitro-Gruppe, R_5O-, R_5CONH-, R_5NHCO-, $(R_5)_2NCO$-, R_SSO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- oder $R_5NHCONH$-, wobei R_5 darstellt eine Alkyl- oder eine Aryl-Gruppe,

zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung von Hyperlipidämie und Arteriosklerose in Säugetieren, bevorzugt Mensch.

4. Verwendung gemäß Anspruch 3, wobei die Verbindung der Formel (I) dargestellt wird durch die folgende Formel (V):



(V)

worin

R_1 darstellt ein Wasserstoffatom, eine Alkyl-, eine Mercapto- oder eine Alkylthio-Gruppe und

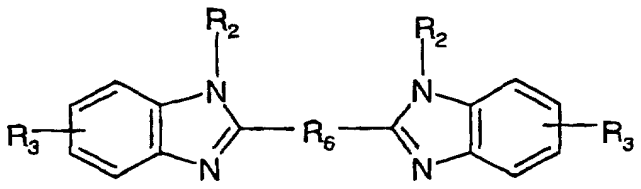
R_3 stellt dar ein Wasserstoffatom, ein Halogenatom, eine Nitro-Gruppe, R_5O-, R_5CONH-, R_5NHCO-, R_5NHSO_2- oder R_5SO_2NH- wobei R_5 eine Alkyl-Gruppe darstellt.

5. Verwendung gemäß Anspruch 4, wobei R_1 darstellt ein Wasserstoffatom, eine Alkyl-Gruppe mit 1 bis 18 Kohlenstoffatomen, eine Mercapto-Gruppe oder eine Alkylthio-Gruppe mit 1 bis 18 Kohlenstoffatomen und R_5 stellt eine Alkyl-Gruppe mit 1 bis 20 Kohlenstoffatomen dar.

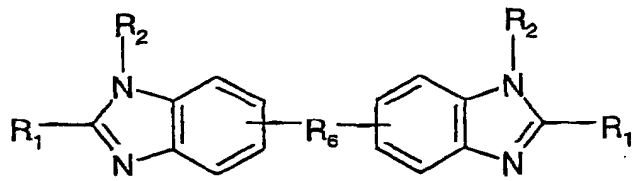
6. Verwendung gemäß Anspruch 5, wobei R_1 darstellt eine Wasserstoffatom, eine Alkyl-Gruppe mit 1 bis 8 Kohlenstoffatomen, eine Mercapto-Gruppe oder eine Alkylthio-Gruppe mit 1 bis 8 Kohlenstoffatomen und R_5 stellt eine Alkyl-Gruppe mit 4 bis 18 Kohlenstoffatomen dar.

Revendications

1. Composition pharmaceutique comprenant un composé de formule (II) ou (III), ou un sel pharmaceutiquement acceptable de celui-ci, ainsi qu'un support ou diluant pharmaceutiquement acceptable :



(II)



(III)

où

R_1 représente un atome d'hydrogène, un groupe alkyle, aryle, mercapto, alkylthio, alcénylthio, arylthio ou hétérocyclo ;

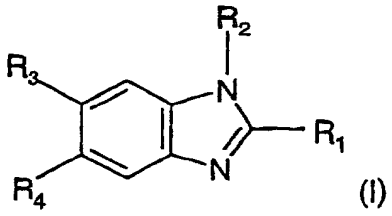
R_2 représente un atome d'hydrogène ou un groupe alkyle, à condition que le groupe alkyle ne soit pas substitué par un groupe hydroxyle ;

R_3 représente un atome d'hydrogène, un atome d'halogène, un groupe nitro, R_5O-, R_5CONH-, R_5NHCO-, $(R_5)_2NCO$-, R_5SO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- ou $R_5NHCONH$- où R_5 représente un groupe alkyle ou aryle ; et

R_6 représente un groupe divalent,

2. Utilisation d'un composé de formule (II) ou (III), ou d'un sel pharmaceutiquement acceptable de celui-ci, selon la revendication 1, pour la fabrication d'une composition pharmaceutique pour traiter l'hyperlipidémie et l'artériosclérose chez les mammifères, de préférence l'homme.

3. Utilisation d'un composé de formule (I) ;



(I)

où

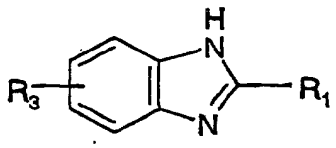
R_1 représente un atome d'hydrogène, un groupe alkyle, mercapto, alkylthio, alcénylthio, arylthio ou hétérocyclo;

R_2 représente un atome d'hydrogène ou un groupe alkyle éventuellement substitué par un groupe aryle, amino ou acylamino ; et à condition que le groupe alkyle ne soit pas substitué par un groupe hydroxyle ; et

R_3 et R_4 représentent chacun indépendamment un atome d'hydrogène, un atome d'halogène, un groupe nitro, R_5O-, R_5CONH-, R_5NHCO-, $(R_5)_2NCO$-, R_5SO_2NH-, R_5NHSO_2-, R_5OCO-, R_5COO- ou $R_5NHCONH$-, où R_5 représente un groupe alkyle ou aryle,

pour la fabrication d'une composition pharmaceutique pour traiter l'hyperlipidémie et l'artériosclérose chez les mammifères, de préférence l'homme.

4. Utilisation selon la revendication 3, où le composé de formule (I) est représenté par la formule (V) suivante :



(V)

où

R_1 représente un atome d'hydrogène, un groupe alkyle, mercapto ou alkylthio ; et

R_3 représente un atome d'hydrogène, un atome d'halogène, un groupe nitro, R_5O-, R_5CONH-, R_5NHCO-, R_5NHSO_2- ou R_5SO_2NH-, où R_5 représente un groupe alkyle.

5. Utilisation selon la revendication 4, où

R_1 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 18 atomes de carbone, un groupe mercapto ou un groupe alkylthio ayant 1 à 18 atomes de carbone ; et

R_5 représente un groupe alkyle ayant 1 à 20 atomes de carbone.

6. Utilisation selon la revendication 5, où

R_1 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 8 atomes de carbone, un groupe mercapto ou un groupe alkylthio ayant 1 à 8 atomes de carbone ; et

R_5 représente un groupe alkyle ayant 4 à 18 atomes de carbone.